REMARKS

Claims 1-14 have been canceled and new claims 15-34 have been added herein.

New claims 15-21 are directed to a drug composition. New claims 22-29 are directed to a nuclear resonance imaging method. New claims 30-34 are directed to a method of confirming a bio-distribution.

Support for new claims 15-34 can be found in the original claims.

With respect to claims 30-34 directed to a method of confirming a biodistribution, support is also found in the specification on page 10, lines 5-11. As described, the drug composition of the present invention is administered and the circulation and distribution of the drug composition in a living body can be simultaneously monitored. Additionally, the present drug composition is useful for the confirmation of the circulation and distribution of the drug composition in a living body beforehand by the administration prior to the full-scale administration of the drug composition. Thus, the present drug composition can be used in the method of confirming a biodistribution of claims 30-34, thereby enabling the selection of a proper medical drug and to estimate its efficacy. Hence no issues of new matter are presented.

The Examiner objected to the specification and required Applicants to provide a substitute specification.

A substitute specification is submitted herewith along with a marked up copy in compliance with 37 C.F.R. § 1.125. The substitute specification does not include any new matter. Applicants respectfully request acceptance and entry of the attached substitute specification. (Will be forwarded to you under separate cover).

Claims 6-14 are objected to as improper multiple dependent claims.

Claims 6-14 are canceled herein and therefore the rejection is moot. Further, none of the new claims 15-34, include multiple dependent claims.

Claims 1-14 are rejected under 35 U.S.C. § 101 allegedly because of the recitation of a use, without setting forth any steps involved in the process.

Claims 1-14 are canceled herein and therefore the rejection is moot. However, Applicants submit that claims 1-14 were directed to a drug composition and not to a process. As discussed previously, new claims 15-21 are directed to a drug composition and new claims 22-34 are method claims which properly recite steps of the claimed method.

Claims 1-14 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. The Examiner sets forth a number of reasons for this rejection on pages 3-4 of the Office Action.

Claims 1-14 are canceled herein and therefore the rejection is moot. However, the rejection is addressed to the extent that the Examiner's reason for rejection may be relevant to new claims 15-34.

In paragraph (iv) on page 3 of the Office Action, the Examiner states that the phrase "the relaxation effect is spreaded" is vague, indefinite and confusing.

New claim 15 recites "the relaxation state spreads" to clarify the claimed invention. In this regard, the H proton directly bonded to $-^{17}OH$, $-^{14}NH$ and $-^{33}SH$ is exchanged with an ambient proton in a vital component of a target organ or tissue, so that the relaxation time of the proton is changed. Further, the relaxation time of the H proton newly bonded to ^{17}O, ^{14}N and ^{33}S is also changed by the exchange. The above-mentioned sequential change of the relaxation time is repeated.

Thus, the H proton sequentially bonded to ^{17}O, ^{14}N and ^{33}S by the exchange with a proton is sequentially affected by the change of the relaxation time with ^{17}O, ^{14}N and ^{33}S. As a result, the proton affected by the change of the relaxation time gradually increases and sequentially spreads.

In paragraph (vi) on page 3 of the Office Action, the Examiner states that the phrase "therapeutic agents nutritional or tonic agents, agents for blood and humor, and agents for diagnosis" is vague and indefinite allegedly because these agents are not defined in the specification.

Applicants respectfully traverse this basis for rejection in view of the disclosure on page 9, at lines 5-12, where examples are provided for the recited agents. Thus, Applicants submit that the claims are definite when read in light of the specification and based upon the interpretation one of ordinary skill in the art would give. Further, Applicants note that the phrase "blood and humor agent" is not recited in the newly added claims.

In paragraph (vii) on page 3 of the Office Action, the Examiner states that the phrase "wherein the agent for blood and humor is infusion" is allegedly vague indefinite and confusing.

Applicants respectfully traverse this basis for the rejection and refer the Examiner to page 12, lines 3-11 where an infusion is described as a substitute for a blood transfusion and further as one of various electrolyte infusions selected depending upon the kind and concentration of the electrolyte used. Further, Applicants note that the phrase "wherein the agent for blood and humor is infusion" is not recited in the present claims.

In paragraph (viii) on page 4 of the Office Action, according to the Examiner, claim 6 is allegedly vague, indefinite and confusing as to whether the compound comprising the ^{17}OH, ^{14}NH or ^{33}SH is the same as the drug or whether the drug comprises the active ingredient, the additive, and the solvent.

In response, Applicants point out that the present invention is directed to a drug composition that contains a compound which comprises at least one member selected from -^{17}OH, -^{14}NH, and -^{33}SH in its structure. Since the invention is a drug composition, the composition must contain an active ingredient. Further, the compound that contains at least one member selected from -^{17}OH, -^{14}NH, and -^{33}SH can be the active ingredient, or can be some other component such as the additive or solvent. *See,* e.g., specification page 6, lines 14-15. Applicants submit that the claims that are now in the present application are clear and would be understood by those of ordinary skill in the art.

In paragraph (ix) on page 4 of the Office Action, the Examiner asserts that the phrase in claim 12 "wherein the drug has been processed with a material for a drug delivery system" is vague, indefinite and confusing as to what is meant by processing a drug and the materials for the drug delivery system. Further, the Examiner stated that the specification does not define this phrase.

Applicants respectfully traverse this basis for rejection. Applicants submit that when read in light of the specification on page 9, second line from the bottom through line 1 of page 10, one of ordinary skill in the art would understand what is meant by the claim language of claim 12. Present claim 20 recites "wherein the composition contains a material for a drug

delivery system". Applicants submit that the claim language of claim 20 is clear and would be understood by one of ordinary skill in the art.

In view of the above, Applicants respectfully request withdrawal of the rejection.

Claims 1-3, 5, 6 and 14 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Hopkins et al. (Mag. Res. In Med.).

According to the Examiner, Hopkins et al teach oxygen-17 compounds as potential NMR T2 contrast agents and the effects of $H_2{}^{17}O$ on protein solutions and living tissues.

Claims 1-14 are canceled herein and therefore the rejection is moot. However, to the extent that the rejection may be relevant to the present claims, Applicants respectfully traverse the rejection.

The present invention is directed to a drug composition selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, containing a compound which comprises at least one member selected from the group consisting of $-^{17}OH$, $-^{14}NH$ and $-^{33}SH$ in its chemical structure, wherein ^{17}O, ^{14}N, or ^{33}S exerts a relaxation effect on the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton, bonded to ^{17}O, ^{14}N or ^{33}S thereby enabling detection by nuclear magnetic resonance, as is defined in new claim 15. Further, the object of the present invention is to provide a physiologically acceptable medical drug which enables external detection of the effective circulation or distribution of the drug, used for a disease, in the target organ or tissue in vivo where it is needed by the nuclear magnetic resonance method before or at the same time as the

administration of a therapeutic agent to each patient, as is disclosed on page 5, line 23 to page 6, line 3 of the specification.

That is, the present drug composition is selected from drugs containing a compound which comprises at least one member selected from the group consisting of the -OH, -NH and -SH groups in its chemical structure, and the whole or a part of the O, N or S atoms constituting the respective groups are substituted with their respective isotopes ^{17}O, ^{14}N or ^{33}S, as is disclosed on page 8, lines 2 to 9 of the specification. When the O, N or S atom, in the drug composition containing a compound which comprises a group selected from -OH, -NH, or -SH as a constituent, is substituted with its stable isotope ^{17}O, ^{14}N or ^{33}S, then the elementary constituents, formulation and composition of the drug composition *per se* are unchanged by said substitution with the stable isotope. As a result, the drug composition, with its isotope, enables the external detection of the effective circulation or distribution of the drug in a target organ or tissue in vivo where it is needed, by a nuclear magnetic resonance imaging method, before or simultaneously with the administration of a therapeutic agent to each patient.

The non-invasive observation of the biodistribution, such as a circulation or distribution of the diagnostic agent in vivo, from outside of a living body is conventionally conducted. For example, when the drug composition contains glucose, 2-fluoro (^{18}F) -2-deoxy-D-glucose is used as a contrast medium for positron emission tomography (PET), as is disclosed on page 3, lines 8 to 20 of the specification. However, a conventional 2-fluoro (^{18}F) -2-deoxy-D-glucose is obtained by introducing the new element (^{18}F) into the glucose. The resulting drug composition containing 2-fluoro (^{18}F) -2 -deoxy-D-glucose is different in the elementary constituents, formulation, composition of the preparation, from the original drug composition containing

glucose. Thus, such a drug composition cannot be used for the observation of biodistribution of the glucose *per se*.

The present drug composition resolves the above-mentioned problems. That is, the present drug composition enables external detection of the effective circulation or distribution of a therapeutic agent used *per se*, in a target organ or tissue in vivo where it is needed, by a nuclear magnetic resonance imaging method, before or simultaneously the administration of the therapeutic agent to each patient.

On the other hand, Hopkins et al disclose that the isotopic enrichment of solutions, living tissues and organisms with ^{17}O in the form of $H_2{}^{17}O$ shortens their proton NMR transverse relaxation times (T_2) and produces changes in NMR image intensity. Hopkins et al teach that the $H_2{}^{17}O$ can be used as contrast agents by administering it to a living body, and certain ^{17}O compounds may be explored as contrast agents in magnetic resonance imaging.

Hopkins et al merely disclose the administration of the $H_2{}^{17}O$-enriched water to a living body, and the observation of the distribution of the $H_2{}^{17}O$ *per se* from outside of the body. Hopkins et al do not mention drugs containing a compound which comprises at least one member selected from the group consisting of the -OH, -NH and -SH groups in its chemical structure. Therefore, Hopkins et al do not disclose that the whole or a part of the O, N or S atoms constituting the respective groups are substituted with their respective isotopes ^{17}O, ^{14}N or ^{33}S, and that the elementary constituents, formulation, composition of the drug composition *per se* are unchanged by said substitution of the stable isotope. Indeed, Hopkins et al are silent as to a drug composition and methods using the composition wherein the drug composition is selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic

agents, and contains a compound which comprises at least one member selected from the group consisting of -^{17}OH, -^{14}NH and -^{33}SH in its chemical structure, wherein ^{17}O, ^{14}N or ^{33}S exerts a relaxation effect on the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton, bonded to ^{17}O, ^{14}N or ^{33}S thereby enabling detection by nuclear magnetic resonance, as recited in the present claims.

Hopkins et al refer to certain compounds incorporating ^{17}O into a larger molecular species, in addition to the $H_2{}^{17}O$. Particularly, Hopkins et al refer to "compounds in which a high percentage of the oxygen is metabolized to water" on page 403, lines 13 to 19 thereof, which means that those compounds essentially need metabolizing in a living body so as to produce the detective $H_2{}^{17}O$, after the administration of those compounds. This is because Hopkins et al are directed to detect the effect of ^{17}O on the proton relaxation times for the H proton of the $H_2{}^{17}O$ *per se*, which is produced during metabolism.

On the other hand, the present drug composition contains a compound which comprises at least one member selected from the group consisting of -^{17}OH, -^{14}NH and -^{33}SH in its chemical structure. Therefore, the ^{17}O, ^{14}N or ^{33}S in the compound can exert a relaxation effect on the H proton bonded thereto immediately after the administration of the drug composition, without undergoing any changes of the compound due to metabolism.

Thus, the compounds incorporating ^{17}O referred to in Hopkins et al are clearly distinguishable from the present drug composition. Hopkins et al neither disclose nor suggest the present drug composition selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, containing a compound which comprises at least

one mater selected from the group consisting of -^{17}OH, -^{14}NH and -^{33}SH in its chemical structure. Thus, the presently claimed invention is not anticipated by Hopkins et al.

Accordingly, Applicants respectfully request withdrawal of the rejection.

Claims 1-14 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Hopkins et al (Mag. Res. In Med.) in view of Unger (6,088,613).

Hopkins et al is applied as discussed above.

According to the Examiner, Hopkins et al fail to teach infusion, sugars, amino acids, aqueous solvents, and drug delivery systems. To remedy this deficiency the Examiner asserts that Unger teaches a method of magnetic resonance focused surgical and therapeutic ultrasound and discloses contrast mediums comprising a gas or gaseous precursor filled vesicle, and optionally a therapeutic compound.

Claims 1-14 are canceled herein and therefore the rejection is moot. However, to the extent that the rejection may be relevant to the present claims, Applicants respectfully traverse the rejection.

Unger (U.S. Patent No. 6,088,613) discloses a method of magnetic resonance imaging focused surgical and therapeutic ultrasound comprising administering a contrast medium for magnetic resonance imaging comprising gas filled vesicles to a patient requiring surgery, using said contrast medium to scan the patient with magnetic resonance imaging to identify the region of the patient requiring surgery, and applying ultrasound to the region to carry out surgery (col. 4, lines 50-57). The vesicle disclosed in Unger comprises a targeting agent, a therapeutic which is released upon application of ultrasound, an oligonucleotide or antisense sequence, an antibody,

a chemotherapeutic agent, a paramagnetic agent, a superparamagnetic agent or the like (claims 5, 6, 7 and 16), and the gas filled in the vesicle is air, nitrogen, carbon dioxide, oxygen, fluorine, helium, argon, xenon or neon (claim 11); gaseous precursor (col. 13, lines 6 to 8); perfluorocarbons (claim 13); ^{17}O (claim 15) or the like. Further, the vesicle disclosed in Unger may be a liposome, monolayer, lipid, polysaccharide or the like (claims 29, 31, 33 and 39).

The Examiner states that, since Unger utilizes the oxygen-17 gas filled vesicles as contrast agents for NMR, one would expect the contrast agents of Unger and Hopkins et al to have similar properties; hence, the replacement of one for the other for imaging purposes would be within skilled of one in the art.

However, as is mentioned above, Unger discloses the use of an encapsulated contrast agents wherein a gas such as ^{17}O or He, Ar, Ne, Xe or the like is filled into a vesicle. That is, the contrast agents disclosed in Unger are insulated from contact with living tissues, organisms and the like under the detection by NMR. Therefore, the method disclosed in Unger is directed to the detection of the signal brought by ^{17}O or He, Ar, Ne, Xe or the like *per se* in the vesicle. Examples 9 and 10 of Unger particularly refer to the NMR method using ^{17}O gas, however, the method merely monitors the signal brought by the ^{17}O itself.

On the other hand, as is mentioned above, Hopkins et al disclose that certain ^{17}O compounds may be explored as contrast agents in magnetic resonance imaging, and the ^{17}O compounds correspond to the ones in which a high percentage of the oxygen is metabolized to water, i.e., the ones metabolized to produce $H_2{}^{17}O$. Hopkins et al intend to monitor the signal brought by the H proton of the $H_2{}^{17}O$ by NMR, by utilizing the change of the proton transverse relaxation times on the basis of the effect of ^{17}O.

Comparing the contrast agents disclosed in Unger and Hopkins et al, Unger monitors the signal brought by the ^{17}O nucleus per se in the contrast agent, while Hopkins et al monitor the signal brought by the H proton of the $H_2{}^{17}O$. Accordingly, the contrast agents disclosed in Unger and Hopkins et al, are quite different from each other, since the contrast agents give the images by different detective methods. Thus, the Examiner' s assertion that the contrast agents of Unger and Hopkins have similar properties is not correct.

The present drug composition, containing a compound which comprises at least one member selected from the group consisting of -^{17}OH, -^{14}NH and -^{33}SH in its chemical structure, is able to exert the relaxation effect on the H proton bonded to the ^{17}O, ^{14}N or ^{33}S in the compound at the time of the administration to a living body. The biodistribution of the drug composition of the present invention can be detected and imaged by the spread of the relaxation effect exerted through the sequential exchange of a proton in a vital component of a target organ or tissue of a living body with the H proton, and is not detected by the signal brought by the ^{17}O nucleus per se.

As is mentioned above, the detective method by NMR as well as the contrast agent are quite different between Unger and Hopkins et al. Thus, one of ordinary skill in the art would not have been motivated to modify or combine the disclosures of Hopkins et al and Unger by replacing one for the other. Further, even if one would try to employ the combination of the contrast agents disclosed in Hopkins et al and Unger by the replacement of one for the other for imaging purpose, one of ordinary skill in the art would not have had a reasonable expectation of achieving the presently claimed drug composition and methods of using the drug composition wherein the drug composition contains a compound which comprises at least one member

selected from the group consisting of -^{17}OH, -^{14}NH and -^{33}SH in its chemical structure and the O, N and S are substituted with its stable isotope of ^{17}O, ^{14}N or ^{33}S respectively, thereby exerting a relaxation effect on the H proton bonded to the ^{17}O, ^{14}N or ^{33}S and spreading the relaxation effect through the exchange of a surrounding proton with said H proton.

Moreover, neither reference teaches nor suggests that the O, N or S atom, in the objective drug composition containing a compound which comprises a group selected from -^{17}OH, -^{14}NH and -^{33}SH, is substituted with its stable isotope ^{17}O, ^{14}N, -^{33}S, wherein the elementary constituents, formulation, composition of the preparation for the objective drug composition per se are unchanged by the substitution of the stable isotope. Thus, one of ordinary skill in the art would not have had a reasonable expectation of achieving the claimed drug composition and methods of using the composition wherein the drug composition selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, containing a compound which comprises at least one member selected from the group consisting of -^{17}OH, -^{14}NH and -^{33}SH in its chemical structure, wherein ^{17}O, ^{14}N, or -^{33}S exerts a relaxation effect on the N proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton, bonded to ^{17}O, ^{14}N, or -^{33}S, thereby enabling external detection by nuclear magnetic resonance imaging.

In view of the above, Hopkins et al and Unger do not teach or suggest, alone or in combination, the presently claimed invention.

Accordingly, Applicants respectfully request withdrawal of the rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

A substitute specification is attached hereto.

IN THE CLAIMS:

Claims 1-14 are canceled.

Claims 15-34 are added as new claims.

IN THE ABSTRACT:

Drugs for medical use characterized by containing a compound which carries in its structure at least one member selected from the group consisting of $-^{17}OH$, $-^{14}NH$, $-^{33}SH$, wherein the above ^{17}O, ^{14}N, or ^{33}S exerts a relaxation effect on the proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body by the above-mentioned proton, thus enabling detection by nuclear magnetic resonance. The effective circulation or distribution of such a physiologically acceptable medical drug in the target organ or tissue in vivo where it is needed can be externally detected by the nuclear magnetic resonance method before or same time as the administration of a therapeutic agent remedy to each patient.

SPECIFICATION

DRUGS FOR MEDICAL USE ENABLING NUCLEAR MAGNETIC RESONANCE DIAGNOSIS BY SCALAR COUPLING

TECHNICAL FIELD

The present invention relates to drugs for medical use which can be detected by the nuclear magnetic resonance method, particularly to drugs for medical use which contain a compound that exerts a relaxation effect on the proton of ^{1}H hydrogen atom in system by ~~the~~ scalar coupling.

BACKGROUND ART

It is acknowledged by everybody that medicines confer great benefits to mankind. However, medicines are not essential components for the maintenance of life and, in the case of a medicine which is a foreign material to a living body, it is not provided with a mechanism of being selectively transported to a target organ or tissue in the body unlike essential components for a living body. Consequently, the medicine administered into a living body comes to distribute itself not only to the intended site but to everywhere in the living body.

Accordingly, many medicines are not only inefficient in efficacy, but cause side effects in greater or lesser extent. Moreover, since the disease state is not uniform for each patient, the distribution state of the medicine becomes~~the~~ more complicated, and it is difficult, for each patient, to select a

truly effective medicine, to predict its effect and to estimate the prognosis including side effect side effects. For example, ~~it is not too much to say that even a dose which is~~ generally ~~called~~the "normal dose" in therapeutic practice ~~has been decided from the result~~is based on the results of clinical trials conducted for only several hundred cases or~~relies upon~~ the results accumulated by the intuition and experience of doctors. Thus, at the present state, there can~~not~~ be found no objective means for suppressing unfavorable effects resulting from unnecessary distribution of a medicine and bringing out the intended effective action thereof to the greatest extent for each patient. That is to say, the problem is that it is yet unknown how and to what extent~~is~~ a medicine is transported to a target organ or tissue.

~~The medical~~Medical treatment of the present day is supported by~~great~~ many peripheral sciences and technologies. Particularly marked is the progress of imaging diagnosis including X-ray diagnosis, nuclear magnetic resonance diagnosis, ultrasonic diagnosis and nuclear medicine diagnosis. Furthermore, various drugs for diagnostic use suited to each of the diagnostic methods ~~have been~~are being developed, and it has become possible to determine ~~grasp from the outside~~externally the in vivo pharmacokinetics, such as circulation and distribution of these drugs for diagnostic use in real time. In such a case, however, though previous drugs for diagnostic use enable accurate specification of the morbid site in the living body and identification of the morbid state based on the in vivo pharmacokinetics thereof, they give virtually no suggestion, after the diagnosis, for the proper selection of therapeutic

drugs to be actually used and for the prediction of their efficacy. Nevertheless, in recent years, for example, as a contrast medium for positron emission tomography (PET), one of the nuclear medicine diagnoses, 2-fluoro(^{18}F)-2-deoxy-D-glucose, which is a glucose-analogue, ~~has come to appear~~appears at the actual spots of medical treatment. However, though it is structurally analogous to glucose, which is an existing drug, it does not reflect the in vivo pharmacokinetics of glucose in a strict sense; further, the object of its use is limited to the diagnosis of tumors or the like, and it is not used as the means for collecting information ~~in~~by using glucose as a drug. Moreover, it has the disadvantage of being radioactive.

Among the several imaging diagnostic methods which enable non-invasive observation of the inside of a living body from the outside, the diagnostic method with nuclear magnetic resonance has a number of merits which are not observed in other methods of imaging diagnosis. In particular, since it gives a high contrast between soft tissues as compared with previous X-ray CT, it has a very high discriminating ability between various soft tissues such as the ones in the brain, heart, liver, kidney and the like. Furthermore, it permits tomography in any desired direction and can ~~afford~~provide blood flow information; these points are favorable in tracing in vivo behavior of drugs. Moreover, the apparatus for nuclear magnetic resonance has already been used in many medical organizations, so that the method is not restricted in its use unlike PET, ~~of~~for which the apparatus is provided only to a limited number of medical organizations.

The principle of the diagnostic method with nuclear

magnetic resonance is as follows: when a high frequency pulse including the resonance frequency of the hydrogen atom ^{1}H is irradiated, a resonance phenomenon takes place at the hydrogen nuclei and the resonance signal is observed. This serves for imaging the state of distribution of the proton of hydrogen present as water in the living body. It is also apparent that the method is free from the risk of radiation exposure unlike the X-ray diagnostic method and nuclear medicine diagnostic method.

It has been reported that an element having a ~~quadrupole~~ quadruple nucleus of a nuclear spin of 1 or more, for example ^{17}O, shortens the transverse relaxation time (T_2), which forms the basis in imaging protons, by ~~the~~ scalar coupling with the proton of hydrogen atom ^{1}H bonded thereto (S. Meiboom, J. Chem. Phys., 39, 375, 1961). Arai et al. have disclosed a method wherein, for the purpose of imaging the distribution of water $H_2{}^{17}O$ formed as a part of the metabolite of $^{17}O_2$ by using the above-mentioned technology, $^{17}O_2$ is mixed with a perfluoro compound and an emulsifier and administered into a living body (Japanese National Publication (Kohyo) 3-500896). However, Arai et al., ~~the said inventors,~~ have mentioned as the result of their later study that the change of signal intensity due to $^{17}O_2$ metabolysis and the condition of metabolic function do not always correspond well to each other, and a good imaging of $H_2{}^{17}O$ of the metabolite cannot be attained (JP-A-6-22936)

Further, some attempts have been made to obtain the image of a proton in high sensitivity by utilizing ~~the~~ scalar coupling. For example, Navon et al. have developed a measuring method using $H_2{}^{17}O$ with ^{17}O irradiation (US5479924).

DISCLOSURE OF THE INVENTION

~~Overcoming~~ In order to overcome the above-mentioned problems that the medical science on individual difference which forms the basis for the differentiation of patients mainly in the therapeutical aspect has not yet been ~~established~~ able to establish scientifically, ~~the~~ an object of the present invention is to provide a physiologically acceptable medical drug which enables external detection of the effective circulation or distribution of the drug, used for a disease, in the target organ or tissue in vivo where it is needed by the nuclear magnetic resonance method before or at the same time as the administration of a therapeutic agent to each patient. Said medical drug can be used in the nuclear magnetic resonance imaging, the nuclear magnetic resonance spectrometry or the determination of relaxation time.

The present inventors have made extensive study to attain the above-mentioned object. As a result, the inventors have found that a medical drug can itself become a pharmacokinetic-~~diagnotic~~ diagnostic agent which can provide for each patient information on the circulation and distribution of the drug in vivo by ~~the~~ a nuclear magnetic resonance method utilizing ~~the~~ scalar coupling when the drug contains, among the constituents contained in the drug, a compound which carries in its chemical structure at least one member selected from the group consisting of -OH, -NH and -SH.

Thus, the present invention provides a drug for medical use characterized by containing a compound which carries in its chemical structure at least one member selected from the group consisting of $-^{17}OH$, ^{14}NH and ^{-33}SH, wherein the above ^{17}O, ^{14}N or

^{33}S exerts a relaxation effect on the proton of hydrogen ^{1}H bonded thereto and the relaxation effect ~~is spreaded~~spreads through the exchange of a proton in a vital component of a target organ or tissue in a living body with the above-mentioned proton, thus enabling detection by the nuclear magnetic resonance method.

The above-mentioned vital component of a target organ or tissue in a living body is usually water, but it may also be lactic acid, N-acetylaspartic acid, etc.

The "detection by the nuclear magnetic resonance method" ~~signifies to measure a~~allows for measurement of phenomenon wherein the ^{17}O, ^{14}N or ^{33}S in the above compound contained in the above-mentioned medical drug exerts a relaxation effect on the proton of hydrogen ^{1}H bonded thereto and then the proton exchanges itself with a proton in a vital component of a target organ or tissue in a living body by means of nuclear magnetic resonance imaging, nuclear magnetic resonance spectrometry or relaxation time measurement each using a proton as the detection nucleus.

According to the present invention, it becomes possible to provide a medical drug which enables external detection of the effective circulation or distribution of the drug, used for a disease, in the target organ or tissue in vivo where it is needed by the nuclear magnetic resonance method before the administration of a therapeutic agent to each patient or in real time, and it becomes further possible to establish the medical science on individual difference which forms the basis for differentiation mainly in the therapeutic aspect.

MODE FOR CARRYING OUT THE INVENTION

The drug for medical use according to the present invention is selected from drugs which contain as a constituent a compound ~~carrying~~having in its chemical structure at least one member selected from the group consisting of the -OH, -NH and -SH groups. Furthermore, the whole or a part of the O, N or S atoms constituting the respective groups are substituted with their respective isotopes ^{17}O, ^{14}N or ^{33}S. Accordingly, said drug for medical use can be synthesized by using a raw material or intermediate, by which the -OH, -NH or -SH group is to be introduced, in which the whole or a part of the O, N or S atoms have been substituted with their respective stable isotopes ^{17}O, ^{14}N or ^{33}S, according to a known method for preparing a medical drug. Though ^{17}O exists in nature only in a low concentration of 0.04%, the separation of ^{17}O and the enrichment of ^{16}O by ^{17}O themselves are not the object of the present invention. With regard thereto, several methods are described in literature which include, for example, fractional distillation of heavy water, electrolysis and laser (isotope) separation.

The selection of the medical drug of the present invention containing a compound, in which the whole or a part of the O, N or S atoms of the -OH, -NH or -SH groups are substituted with their respective stable isotopes ^{17}O ^{14}N or ^{33}S can be made by those skilled in the art within the range not deleterious to the object of the present invention, and any desired existing medical drug can be used according to the therapeutical or diagnosis object. More specifically, selection may be made as desired according to the disease state of each patient from therapeutic agents, such as drugs for the central nervous system, drugs for

the circulatory system, drugs for the digestive system, drugs for the urogenital system and drugs for tumors; nutritional or tonic agents; agents for blood and humor such as infusion; or agents for diagnosis, such as X-ray contrast media, MRI contrast media, ultrasonic contrast media and radiopharmaceuticals. Since ^{17}O and ^{33}S, which are each a stable isotope element, have respectively exactly the same chemical properties as those of usual oxygen ^{16}O and sulfur ^{32}S, ^{17}O and ^{33}S do not show pharmacokinetics of a different nature also in a living body. The above-mentioned compound to be substituted may be any of the active ingredients of medical drugs, additives and solvents. Specifically, the active ingredient is preferably a sugar, particularly glucose, amino acid, etc; the solvent is preferably an aqueous solvent, particularly water. They may be compounded according to the formulation ratio of respective medical drugs. The dosage form may also be selected according to the respective medical drugs and may be either a solution or a lyophilized product which is dissolved before use. Further, it may have been processed with a material for a drug delivery system, such as a liposome or the like.

The medical drug thus obtained is administered according to the administration routes determined for respective medical drugs. It is administered, for example, intravenously, intraarterially, intramuscularly or orally, but it may be administered precutaneously as the occasion demands. When it is desired to select a proper medical drug or to estimate its efficacy, the medical drug of the present invention may be administered ~~in advance~~ prior to the full-scale administration of a medical drug. When it is desired, for example, to monitor

~~simultaneously with~~ the administration of a therapeutic agent and whether a medical drug is properly circulated or distributed in a target organ or tissue, simultaneously, the medical drug of the present invention may be used as the whole or a part of the medical drug.

The dose of the medical drug of the present invention may be appropriately selected according to the ~~uses~~ use of the drug, the degree of enrichment of ^{17}O, ^{14}N or ^{33}S, and the kind of the nuclear magnetic resonance method used as the means of determination. The nuclear magnetic resonance method used as the means of determination may be any desired one so long as it is a nuclear magnetic resonance method using a proton as the detection nucleus~~,~~. ~~but it is preferably nuclear~~ Nuclear magnetic resonance imaging, nuclear magnetic resonance spectrometry or relaxation time determination~~,~~ is preferable. ~~particularly preferable being nuclear~~ Nuclear magnetic resonance imaging~~, which is in general use~~is particularly preferred. In an experiment ~~on~~ to determine the distribution of $H_2{}^{17}O$ (^{17}O content: about 89%) using a rat cerebral ischemic model conducted by the present inventors as an experimental example ~~which is instructive in practice~~, an image based on tissue infusion difference ~~could be~~ was obtained by the T2-weighted spin echo method (nuclear magnetic resonance imaging using a proton as the detection nucleus), which is a common imaging method in medical diagnosis. Further, for example, ~~a~~ nuclear magnetic resonance imaging ~~with~~ using ^{17}O irradiation ~~may be~~ is more preferably used since a more enhanced sensitivity can be obtained.

For example, in the percutaneous local therapy (PEIT) of hepatic cancer, wherein pure ethanol is injected

percutaneously and transhepatically into hepatic cancer cells to coagulate and necrotize the cancer cells, there is a high possibility of the ethanol diffusing excessively to cause coagulation and necroses even of the normal hepatic cells. In such a case, for example, by injecting ~~under a nuclear magnetic resonance apparatus~~ the present medical drug obtained by substituting the whole or a part of the ^{16}OH group of ethanol with ^{17}O, under a nuclear magnetic resonance apparatus, and observing the resulting image, ~~a therapy in which the injection range is limited only to cancer cells~~ it becomes possible to provide a therapy which limits the injection range to only cancer cells. Sodium hyaluronate, which is administered into cavitas articulare in the case of osteoarthritis of the knee, can be used, for example, for similar purposes.

On the other hand, in the case of an infusion, which is used as the substitute of a blood transfusion from the viewpoint of replenishing water, it is important how it spreads throughout a living body. In the case of an electrolyte infusion, which ~~is~~ can be of many varieties according to the kind and the concentration of the electrolyte contained therein, a proper drug must be selected for each patient to improve the disease state. In ~~such an~~ this instance, by using the present drug in which the whole or a part of water as a solvent has been substituted with ^{17}O, it becomes possible to judge an electrolyte infusion ~~of~~ and determine what composition is to be used for improving the disease state of each patient.

EXAMPLES

The present invention is described in detail below with

reference to the Examples, but the technical scope of the present invention is not limited thereby.

Example 1 Synthesis of [3-^{17}OH]glucose

20 g (0.07 mol) of methyl-4,6-O-benzylidene-α-D-allopyranoside was dissolved in 108 ml of pyridine to obtain a pale yellow solution. While the solution was being cooled, 43 g (0.23 mol) of p-toluenesulfonyl chloride was added thereto over 15 minutes or more, and the resulting mixture was stirred at 30°C for 48 hours. The reaction solution turned light brown and formed a white precipitate. The reaction solution was poured into ice water and extracted with chloroform. The chloroform layer was separated and washed successively with 5% sulfuric acid, 4% aqueous sodium hydrogen carbonate solution and water. Then the chloroform layer was dried over $MgSO_4$ and evaporated to dryness. The yellow sirupy residue was recrystallized from ethanol to obtain 32 g of a white solid. Yield 79%.

31 g (0.05 mol) of the 2,3-bis(O-p-toluenesulfonyl) derivative obtained above was dissolved in 350 ml of chloroform, and a mixture of 35 ml of a 28% sodium methoxide methanol solution and 65 ml of methanol was added thereto. The resulting mixture was kept at room temperature for 48 hours while being gently stirred and then diluted with 300 ml of water. The chloroform layer was separated, washed twice with water, then dried over $MgSO_4$ and evaporated to dryness. The residue obtained was crystallized from chloroform-ether to obtain a white solid.

The 500 ml of THF was added to 5.29 g (20 mmols) of methyl-2, 3-anhydro-4, 6-O-benzylidene-α-allopyranoside obtained above. While the resulting mixture was being stirred, 1 g of Nafion-H and 1 g of water (^{17}O content: 10%) were slowly added

thereto, and the mixture was stirred overnight at room temperature. The insolubles and Nafion-H were removed by suction filtration and the filtrate was evaporated to dryness under reduced pressure to obtain a white solid. The white solid was hydrolyzed to obtain 1.4 g of [3-^{17}OH] glucose.

Example 2 Preparation of agent for humor stoperative restoring liquid) using water (^{17}O) as solvent

The titled drug was prepared according to the formulation of "KN replenisher 4A" (a trade name, mfd. by Otsuka Pharmaceutical Factory, Inc.), which is a postoperative restoring liquid used as the replenishing agent for water and electrolytes for the whole body early after the operation. Water (^{16}O) was added to 0.234 g of sodium chloride, 8.002 g of glucose and sodium lactate to make up the total to 100 ml. To a 0.5 ml portion thereof was added an equal quantity of water containing 10.5% of ^{17}O so as to prepare an ^{17}O water-containing KN replenisher 4A (^{17}O content: 5.25%)

Example 3 Phantom imaging of aqueous [1-^{17}OH] glucose solution

Water was added to [1-^{17}OH] glucose available on the market so as to prepare a solution of a concentration of 62.55 mg/ml. As a control, glucose (^{16}O) was used to prepare a solution of a concentration of 62.9 mg/ml. These solution solutions were respectively sealed into glass tubes and imaged with a nuclear magnetic resonance imaging apparatus of 2 tesla, Omega CSI. When the echo time was set at 200 msec, the signal intensity ratios of the aqueous [1-^{17}OH] glucose solution and the aqueous (^{16}O) glucose

solution were respectively 79.3 and 93.1. Thus, it has become apparent that [1-^{17}OH] glucose can be a compound which exerts a relaxation effect by ~~the~~ scalar coupling on the water protons of the tissue in which they are distributed.

Example 4 Determination of relaxation time of body liquid drug (postoperative restoring liquid) using water (^{17}O) as solvent

The relaxation time of the (^{17}O) water- containing KN replenisher 4A (^{17}O) content: 5.25%) obtained in Example 2 was determined. As the control, a KN replenisher 4A (^{17}O content: natural abundance ratio) prepared by using water (^{16}O) alone as the solvent was used. The relaxation time was determined by the CPMG method using a Model JNM-FSE-60 pulse NMR. As the result, the relaxation time of the ^{17}O water-containing KN replenisher 4A was 181.19±0.50 msec, being significantly shortened as compared with the relaxation time, 626.36±1.01 msec, of the ^{16}O water-containing replenisher 4A. From the result, it has become apparent that an effective medical drug ^{17}O water-containing KN replenisher 4A which could exert a relaxation effect on a water proton by ~~the~~ scalar coupling could be prepared.

Example 5 Determination of relaxation time of pure ethanol (^{17}OH) in water

A 0.2 ml portion of pure ethanol (^{17}OH, ^{17}O content: 10%) available on the market was mixed with 0.2 ml of water (^{16}O) (50% in terms of ethanol concentration) As a control, a solution

was prepared by mixing pure ethanol (^{16}OH) in the same manner as above. The relaxation times of the two samples thus prepared were determined by the CPMG method using a Model JNN-FSE-60 pulse NMR. As the result, the relaxation time of the pure ethanol (^{17}OH) dilution water was 420.22±0.99 msec, being significantly shortened as compared with the relaxation time (779.12±4.91 msec) of pure ethanol (^{16}OH) of the control. From the result, it ~~has become~~ is apparent that pure ethanol (^{17}OH) can become a medical drug which, after ~~administered~~ administration and ~~when distributed~~ distribution, exerts a relaxation effect on the water proton of a tissue by ~~the~~ scalar coupling.